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EDITORIAL COMMENT

The Emerging Role of Statins in the Treatment of Heart Failure*

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Several retrospective studies have suggested that the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) may benefit patients with ischemic and nonischemic cardiomyopathy (1–5). However, there are limited prospective data to suggest that statins are beneficial once heart failure (HF) is established (6,7). Moreover, there are theoretic concerns that the routine use of statins may be harmful in patients with HF. That is, one explanation for the observation that low circulating levels of cholesterol are associated with worse outcomes in patients with HF (8–10) is that circulating lipoproteins bind bacterial endotoxins that have been absorbed from the edematous gut of HF patients (the endotoxin-lipoprotein hypothesis) (11), thereby preventing endotoxin-induced inflammation from occurring. Theoretically, the lipid-lowering effect of statins might be deleterious by allowing unbound endotoxin to activate immune cells to produce proinflammatory cytokines (tumor necrosis factor [TNF], interleukin [IL]-1, and IL-6), which in turn might contribute to HF progression. Another theoretic problem with the use of statins in HF is related to statins' inhibitory effects on ubiquinone (CoQ10) synthesis, which might precipitate or aggravate HF by creating problems with mitochondrial respiration (12). Thus, the safety and efficacy of statin use in HF is not clearly known.

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In this issue of the *Journal,* Sola et al. (13) report on the results of a prospective double-blind placebo-controlled study in which they randomized 108 patients (New York Heart Association [NYHA] functional class II to IV) with non-ischemic HF and a left ventricular (LV) ejection fraction (EF) of <35% to atorvastatin (20 mg/day) or placebo for 12 months. These authors observed that LV EF increased significantly in the atorvastatin group over the 12-month follow-up period (0.33 ± 0.05 to 0.37 ± 0.04), whereas patients in the placebo group experienced a decline in EF during the same period (0.33 ± 0.04 to 0.31 ± 0.03). In addition, the LV end-diastolic dimensions decreased significantly in the cohort of patients treated with atorvastatin (57.1 ± 5.9 mm to 53.4 ± 5.1 mm), whereas LV end-diastolic dimension increased in the placebo group (56.1 ± 5.9 to 60.3 ± 5.1). The authors further noted that there was an increase in erythrocyte superoxide dismutase activity and significant reductions in serum levels of high sensitivity C-reactive protein (hsCRP), IL-6, and the type 2 tumor necrosis factor receptor in the atorvastatin group, consistent with a decrease in oxidative stress and inflammation. In a related paper also in this issue of the *Journal,* Bleske et al. (14) report on a smaller study to determine the effect of aggressive statin therapy on patient safety and surrogate biomarkers for HF. These authors randomized 15 patients (NYHA functional class I to III) with nonischemic cardiomyopathy into a double-blinded, placebo-controlled crossover trial. Patients already receiving maximal medical therapy were treated with 80 mg of atorvastatin or matching placebo for a 12-week period, with a minimum of an 8-week washout period. Bleske et al. (14) evaluated biomarkers that reflected cardiac remodeling (N-terminal-pro brain natriuretic peptide), inflammation (hsCRP, the type 1 tumor necrosis factor [TNF] receptor), and endothelial activation (vascular adhesion molecule-1, intercellular adhesion molecule-1, soluble P-selectin). Although treatment with high-dose atorvastatin was safe and resulted in a significant decrease in low-density lipoprotein (LDL) concentrations (110 ± 27 mg/dl to 55 ± 18 mg/dl), there were no significant differences between atorvastatin and placebo with respect to the surrogate biomarkers that were measured. Before addressing what these studies tell us about the potential role of statins in the treatment of patients with HF, it is useful to digress for a moment in order to discuss what is know about the biologic properties of statins, as well as the clinical effects of statins in HF that have been observed thus far.

Evidence for the beneficial effects of HMG-CoA reductase inhibitors in experimental models and clinical trials of HF. As shown in Figure 1, HMG-CoA reductase inhibitors lower plasma cholesterol levels by inhibiting HMG-CoA reductase, the rate-limiting enzyme in the mevalonate pathway that is responsible for cholesterol synthesis. Importantly, intermediate products in the mevalonate pathway include isoprenoids such as farnesylpyrophosphate (farnesyl-PP) and geranylgeranylpyrophosphate (geranylgeranyl-PP), which have been linked to activation of downstream signaling pathways mediated by Ras and Rho, respectively. The Ras family of proteins is responsible for cell proliferation and hypertrophy, whereas the Rho family of proteins is important for superoxide generation and cytoskeletal formation (15,16). Rho inhibition has also been linked to increased expression of endothelial nitric

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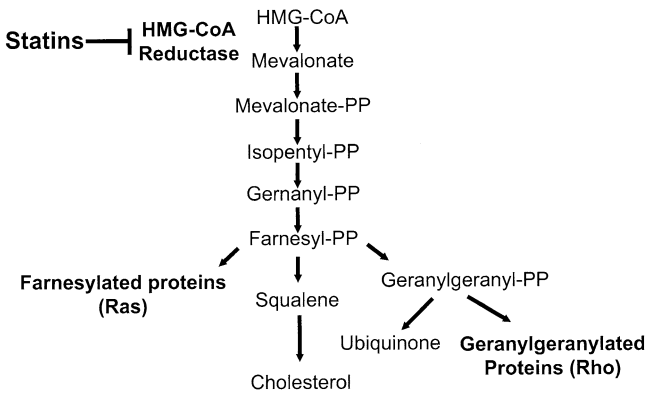

Figure 1. The mevalonate pathway leads to the synthesis of cholesterol. Important intermediate products in the mevalonate pathway include isoprenoids such as farnesylpyrophosphate (farnesyl-PP) and geranylgeranylpyrophosphate (geranylgeranyl-PP), which have been linked to activation Ras- and Rho-mediated signaling. 3-hydroxy-3methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors decrease the synthesis of isoprenoids as well as cholesterol by blocking HMG-CoA reductase.

oxide synthesis, which has a beneficial effect on endothelial function through increased nitric oxide production. Although the mechanism is less clear, statins also activate the phosphatidylinositol 3′- kinase/Akt pathway, which is coupled to cytoprotective signaling pathways (17). On the basis of the foregoing arguments, the lipid-independent effects of statins would be expected to be beneficial in HF patients.

Experimental models. Experimental infarct studies have shown that treatment with statins leads to attenuation of LV remodeling and improved LV ejection performance without directly affecting infarct size. The attenuation in LV remodeling was attributed to decreased cardiac myocyte hypertrophy, decreased activation of matrix metalloproteinases, and decreased fibrosis (18). Importantly, statins have also been shown to promote angiogenesis (19), mobilize bone marrow endothelial progenitor cells (20), result in down-regulation of angiotensin type 1 receptors (21), and lead to improved heart rate variability and baroreflex sensitivity (22,23), any or all of which may have additional beneficial effects on cardiac remodeling.

Clinical trials. Several retrospective analyses of clinical trial databases have suggested that, for patients with coronary artery disease, the use of statins has either reduced the incidence of HF (3) or reduced the mortality of patients with known HF (24,25). Given the known salutary effects of statins on outcomes in coronary artery disease, as well as the high prevalence of ischemic heart disease in HF trials, these findings are not surprising. More interesting, perhaps, is a recent study by Node et al. (7), which provides provisional evidence for the beneficial lipid-independent effects of statins in HF patients. The authors showed that patients (n = 51) with symptomatic nonischemic dilated cardiomyopathy (NYHA functional class II to III) who were randomized to simvastatin for 14 weeks had an improvement in NYHA functional class; improved LV function; and significant decreases in circulating levels of plasma TNF, IL-6, and brain natriuretic peptide. In a smaller study, Laufs et al. (6) randomized 15 patients with non-ischemic dilated cardiomyopathy (NYHA functional class II to III) to cerivastatin (0.4 mg) or placebo for an average treatment period of 20 weeks. They observed that statin treatment resulted in an improvement in quality of life and exercise capacity that was accompanied by decreased plasma concentrations of troponin T, hsCRP, plasminogen activator inhibitor-1, and TNF. Finally, in a retrospective analysis of their cardiac transplant database (n = 551 patients), Horwich et al. (1) showed that statin use was associated with improved survival without the necessity for urgent heart transplantation in both ischemic and nonischemic HF (hazard ratio 0.41, 95% confidence interval 0.18 to 0.94). Thus, the results of the present study by Sola et al. (13) are consistent with previous observational and prospective studies that have shown beneficial effects of statins in HF patients. Moreover, this study extends prior observations by demonstrating that treatment with statins leads to "reverse" cardiac remodeling and suggests (but does not prove) that the anti-inflammatory effects of statins may be through a reduction in oxidative stress. In contrast, the study by Bleske et al. (14) suggests that high-dose atorvastatin for a shorter duration of time was safe but had no effect on HF biomarkers. Although the reasons for these discrepant findings are not known, the most logical explanation (aside from the small numbers of patients) is that the patient cohort studied by Bleske et al. had relatively mild HF and thus had minimal activation of neurohormonal and inflammatory systems. Indeed, as noted by Bleske et al. (14), the biomarkers chosen were "for the most part. . .in the range that. . .was considered normal" (14). Thus, on the basis of the study design that was employed, one would not have expected to have observed striking changes in the panel of biomarkers following statin treatment. Importantly, however, there were no obvious harmful effects of high-dose statins, despite the significant lipid lowering that was observed.

Is there sufficient evidence to warrant the routine use of statins in patients with HF? There is substantial clinical evidence that statins reduce the incidence of HF in patients with known coronary artery disease by reducing coronary events. Moreover, the increasing use of lipid-lowering strategies in recent HF trials has not resulted in worsening outcomes for the subsets of patients treated with statins. Accordingly, the use of statins can be advocated in patients with HF with known coronary artery disease and elevated levels of LDL, as recommended by current practice guidelines. However, the broader question of whether statins should be routinely used in all patients with HF, including patients with ischemic HF with low or normal LDL levels and/or non-ischemic HF, remains unanswered. Given that our randomized clinical experience with statins in nonischemic cardiomyopathy is limited to several small trials in which <100 patients have actually been treated, and given that we have no information with respect to the correct dose of statins to use in these patients, it is premature to

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recommend the routine use of statins for all HF patients. Fortunately, there are several ongoing large-scale clinical outcome trials in HF patients (COntrolled Rosuvastatin multiNAtional trial in heart failure [CORONA], Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca [GISSI-HF] [Italian Group for the Study of the Survival in Cardiac Insufficiency], and RosUvastatiN Impact on VEntricular Remodelling lipidS and cytokines [UNIVERSE]) that should provide a more definitive answer to this important question. Although predicting outcomes of ongoing clinical trials in HF is generally fraught with peril, the results of the study by Sola et al. (13) in the current issue of the *Journal,* as well as the burgeoning experimental and clinical evidence supporting the safety and utility of statins in patients with advanced HF, suggest that statin therapy will find much broader applicability in the standard treatment of HF patients in the foreseeable future.

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REFERENCES

1. Horwich TB, MacLellan WR, Fonarow GC. Statin therapy is associated with improved survival in ischemic and non-ischemic heart failure. J Am Coll Cardiol 2004;43:642–8.
2. Mozaffarian D, Nye R, Levy WC. Statin therapy is associated with lower mortality among patients with severe heart failure. Am J Cardiol 2004;93:1124–9.
3. Kjekshus J, Pedersen TR, Olsson AG, Faergeman O, Pyorala K. The effects of simvastatin on the incidence of heart failure in patients with coronary heart disease. J Card Fail 1997;3:249–54.
4. Hognestad A, Dickstein K, Myhre E, Snapinn S, Kjekshus J. Effect of combined statin and beta-blocker treatment on one-year morbidity and mortality after acute myocardial infarction associated with heart failure. Am J Cardiol 2004;93:603–6.
5. Tousoulis D, Antoniades C, Bosinakou E, et al. Effects of atorvastatin on reactive hyperemia and inflammatory process in patients with congestive heart failure. Atherosclerosis 2005;178:359–63.
6. Laufs U, Wassmann S, Schackmann S, Heeschen C, Bohm M, Nickenig G. Beneficial effects of statins in patients with non-ischemic heart failure. Z Kardiol 2004;93:103–8.
7. Node K, Fujita M, Kitakaze M, Hori M, Liao JK. Short-term statin therapy improves cardiac function and symptoms in patients with idiopathic dilated cardiomyopathy. Circulation 2003;108:839–43.
8. Rauchhaus M, Clark AL, Doehner W, et al. The relationship between cholesterol and survival in patients with chronic heart failure. J Am Coll Cardiol 2003;42:1933–40.
9. Richartz BM, Radovancevic B, Frazier OH, Vaughn WK, Taegtmeyer H. Low serum cholesterol levels predict high perioperative mortality in patients supported by a left-ventricular assist system. Cardiology 1998;89:184–8.
10. Horwich TB, Hamilton MA, MacLellan WR, Fonarow GC. Low serum total cholesterol is associated with marked increase in mortality in advanced heart failure. J Card Fail 2002;8:216–24.
11. Rauchhaus M, Coats AJ, Anker SD. The endotoxin-lipoprotein hypothesis. Lancet 2000;356:930–3.
12. Marz W, Siekmeier R, Muller HM, Wieland H, Gross W, Olbrich HG. Effects of lovastatin and pravastatin on the survival of hamsters with inherited cardiomyopathy. J Cardiovasc Pharmacol Ther 2000;5:275–9.
13. Sola S, Mir MQS, Lerakis S, Tandon N, Khan BV. Atorvastatin improves left ventricular systolic function and serum markers of inflammation in nonischemic heart failure. J Am Coll Cardiol 2006;47:332–7.
14. Bleske BE, Nicklas JM, Bard RL, et al. Neutral effect on markers of heart failure, inflammation, endothelial activation and function, and vagal tone following high-dose HMG-CoA reductase inhibition in non-diabetic patients with non-ischemic cardiomyopathy and average low-density lipoprotein level. J Am Coll Cardiol 2006;47:338–41.
15. Liao JK. Isoprenoids as mediators of the biological effects of statins. J Clin Invest 2002;110:285–8.
16. Laufs U, Liao JK. Isoprenoid metabolism and the pleiotropic effects of statins. Curr Atheroscler Rep 2003;5:372–8.
17. Shiga N, Hirano K, Hirano M, Nishimura J, Nawata H, Kanaide H. Long-term inhibition of RhoA attenuates vascular contractility by enhancing endothelial NO production in an intact rabbit mesenteric artery. Circ Res 2005;96:1014–21.
18. Hayashidani S, Tsutsui H, Shiomi T, et al. Fluvastatin, a 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitor, attenuates left ventricular remodeling and failure after experimental myocardial infarction. Circulation 2002;105:868–73.
19. Kureishi Y, Luo Z, Shiojima I, et al. The HMG-CoA reductase inhibitor simvastatin activates the protein kinase Akt and promotes angiogenesis in normocholesterolemic animals. Nat Med 2000;6:1004–10.
20. Futterman LG, Lemberg L. Cardiac repair with autologous bone marrow stem cells. Am J Crit Care 2004;13:512–8.
21. Strehlow K, Wassmann S, Bohm M, Nickenig G. Angiotensin AT1 receptor over-expression in hypercholesterolaemia. Ann Med 2000;32:386–9.
22. Pliquett RU, Cornish KG, Peuler JD, Zucker IH. Simvastatin normalizes autonomic neural control in experimental heart failure. Circulation 2003;107:2493–8.
23. Pliquett RU, Cornish KG, Zucker IH. Statin therapy restores sympathovagal balance in experimental heart failure. J Appl Physiol 2003;95:700–4.
24. Seal R, Pitt B, Poole-Wilson P, Sharma D, Bradstreet DC, Ikeda LS. Effects of HMG-CoA reductase inhibitors (statins) in patients with heart failure. Eur J Heart Fail 2000;2:96.
25. Hognestad A, Myhre E, Sentralsykehus V-A, Snapinn S, Kjekshus J. Early lipid lowering and beta-receptor blockade during acute myocardial infarction reduce death and non-fatal infarction in heart failure patients (abstr). Circulation 2001;104:A762.